REMARKS

Claims 245-251 are pending in the above-referenced application. Claim 245 has been amended above. No claims have been added or canceled by this paper. Accordingly, claims 245-251 are presented for further examination.

Double Patenting

Claims 245-247 have been provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 255, 257 and 259 of copending Application No. 08/978,636. Although the conflicting claims are not identical, they are considered not to be patentably distinct from each other for the same reasons of record as stated in the first Official action mailed 02/16/99.

The double patenting rejection will be addressed upon indication of allowable subject matter.

The Rejections Under 35 U.S.C. 112, First Paragraph-Lack of Enablement

Claims 245-251 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the same reasons of record set forth in the Official action mailed 02/16/99. It is specifically asserted that Applicant's response provides only an assertion that an ordinarily skilled artisan, armed with the specification, could practice the invention without undue experimentation. This assertion, without any supporting evidence, fails to

overcome the prima facie case of lack of enablement. It is specifically stated in the February 16, 1999 Office Action dated February 16, 1999 that

> Claims 245-251 are further broadly drawn to the process of expressing a nucleic acid product in a cell which includes a "processing elements" that is "substantially removed during processing" in a "compatible cell." The language ' processing element" reads on expression of any gene from said construct that as a "processing" function in a cell, for example, any ribozyme, polymerase, or any protein causing a modification of any molecules (protein or DNA) in cell. The scope of the genus sought for the process of expression of such constructs is not enabled in view of the lack of specificity of guidance in the specification as filed. The specification teaches only prophetically an intron containing polymerase wherein the intron is removed in a compatible cell. The specification does not exemplify application of the T7 polymerase/U1-A, B, C vector as described in example 19 in cells. It appears that only the U1A, B, C clone co-expressed with T7 polymerase (on another vector) is exemplified in the HIV challenge and LacZ assays.
>
> Furthermore, the claims specify the context for producing the product in the cell and no exemplification of whole organism success is found in the specification as filed. There is a high level of unpredictability in the antisense art and analogous gene therapy art for *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target sites in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Despite the synthesis of more resilent, nucleus resistant, oligonucleotide backbones and isolated successes with antisence therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and futher such that antisense and other effects can routinely be obtained. Note Flanagan et al. who teach "although numerous reports have cited antisenses effects using oligonucleotides added to cell medium, direct proof that oligonucleotides enter cells and effect gene inhibition by antisense mechanism is still lacking (page 48, column I)."

> Specifically, *in vitro* results with one antisense molecule are not predictive of *in vivo* (whole organism) success. *In vitro*, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. ((Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo*: it "is very difficult to predict that portions of an RNA molecule will be accessible *in vivo,* effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." And in the instant case, the claims read broadly on administration of an antisense inhibitor in any cell, therefore the whole organism included. (While the specification teaches cell culture inhibition, no evidence of successful *in vivo* (whole organism) antisense inhibition has been shown, nor do the culture examples correlate with whole organism delivery.
>
> One of skill in the art would not accept on its face the successful delivery of the disclosed antisense molecules in vivo in view of the lack of guidance in the specification and the unpredictability in the art. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo,* (2) effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecules into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable and the art as discussed supra. The lack of teaching of these factors in inhibition of the target, coupled to the amount of "trial and error" experimentation involved in the deduction of these results would lead one skilled in the art to necessarily practice an undue amount of experimentation *in vivo.*

Applicants respectfully traverse the rejection. First, in Applicants' view, it would not require undue experimentation for the ordinary skilled artisan to practice the invention. A sufficiently detailed description is provided in the specification for practicing the method of the present invention. Specifically, on page 83, lines 5-7,

a "processing element" is defined as "an RNA processing element including but not limited to an intron, a polyadenylation signal and a capping element, or combinations of the foregoing". A compatible cell is described on pages 87-90. A specific example is described on page 89, where an intron is introduced into the coding sequence of T7 RNA polymerase. It is pointed out that

> [t]his allows the construction of a single construct that contains both the T7 RNA polymerase and, for example, antisense directed by a T7 promoter, with lethality to an incompatible cell being avoided by introduction of the heterologous processing element into the polymerase coding sequence. In a compatible cell, normal expression of the polymerase will occur but lethality should be negated by the nature of its environment.

Furthermore, a description of the method of the present invention is provided on page 83, line 13 to the bottom of page 84:

> Also provided by this invention is a process for selectively expressing a nucleic acid product in a cell, the product being such that further processing is required for its functioning. The process comprises as its first step providing a nucleic acid construct which when introduced into a cell produces a nucleic acid product comprising a non-native processing element, which when in a compatible cell, the processing element being substantially removed during processing. The second step comprises introducing this construct into the cell. The processing element, e.g., an RNA processing element, the nucleic acid product and the steps of introducing the construct in vivo and ex vivo are as described previously. . . .
>
> The present invention provides a universal method for utilizing processing elements, including heterologous elements, for conditional gene inactivation. Rather than a restriction enzyme site, the frequently occurring sequence (C/A)AGG post splice junction sequence is used as te insertion site. This site results from the consensus sequence resulting from an excision of an intron. The consensus splice sequence for splice donors is (C/A)AG*GU and the consensus sequence for splice acceptors (U/C)nN(C/U)AG*G where * represents the splice site (Reference omitted). The frequent occurrence of this

> sequence provides numerous potential sites for the insertion of processing elements. Insertion at any of these sites in a gene coding region should not affect subsequent removal of the processing element in a compatible cell.

A specific embodiment of the present invention is described on page 146-152.

In response to the assertions made in the Office Action regarding enablement of the method of the present invention with respect to whole organisms, Applicants note that Branch and Flanagan were actually published **after** the priority date of the above-referenced application. The MPEP in Section 2164.05(a) states that "the state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date." This section further states "In general, the examiner should not use post-filing date references to demonstrate that the patent is no-enabling." Applicants nevertheless assert that there are a number of publications available as of the priority date of the above-referenced application as well as publications published after the priority date of the above-referenced application which express a more optimistic attitude regarding the suitability of antisense to become useful in therapeutic application. One example of such a publication is Crooke, 1994, Antisense Research and Development 4:145-6, attached hereto as Exhibit 1. Another example is Liu et al, 1997, J. Virol. 71:4079-4085, attached hereto as Exhibit 2 which discloses Tat-activated expression of chloramphenicol acetyltransferase was shown to be specifically inhibited in cells expressing Tat and transactivation response region antisense sequences.

It is also Applicants' position that *in vivo* data is not necessary. As noted in the MPEP Section 2107.03, III, "Office personnel should be careful not to find evidence unpersuasive simply because no animal model for the human disease condition had been established prior to the filing of the application. However,

Applicants note that clinical trials were underway by the assignee of the instant application around the priority date of the above-referenced application. A press release dated July 10, 1996 is attached hereto as Exhibit 3. The results to date have generally been favorable and are publicly available.

In view of the above arguments, Applicants assert that the rejections have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

The Rejections Under 35 U.S.C. §102

As will be described in further detail below, the claims were rejected over Sullenger et al. ("Sullenger"), Hurwitz et al. ("Hurwitz") and DeYoung et al. ("DeYoung").

Sullenger

Claims 245-251 are rejected under 35 U.S.C. §102(e) as being anticipated by Sullenger. It is asserted that Applicants do not suggest how the material elements taught by Sullenger do not share material identity with the scope of possible constructs instantly claimed. Further, it was asserted in the Office Action dated 2/16/99, that Sullenger teaches a method of expression of RNA-based inhibitors of viral replication by localization of an inhibitory RNA such as a ribozyme to a cellular target. Further, the Examiner states that ribozymes are known in the art to have a processing function and also have an inherent half-life and are therefore removed.

Applicants respectfully traverse the rejection. The construct used in the method of the present invention can be distinguished from the expression vector disclosed by Sullenger. The expression vector comprises a nucleic acid sequence

encoding a therapeutic agent comprising a localization signal which acts to localize the therapeutic agent to a specific site within a cell. "Localization signals" are defined in column 3 as

> signals which cause the molecule to which they are attached to become localized in certain compartments, and can be readily discovered using standard methodology. These localization signals may be tethered to the therapeutic agent by any desired procedure, for example, by construction of a DNA template which comprises both the localization signal and therapeutic agent RNA as part of the same RNA molecule, or by covalent or ionic bond formation between two moieties..

The constructs used in the method of the present invention recited in claims 255-260 do not contain such a localization signal. In contrast, the constructs used in the method of the present invention comprise a nucleic acid product comprising a non-native processing element. This processing element is substantially removed during processing. The "localization signal" described in Sullenger et al. would not be considered to be a processing element. The expression vectors disclosed by Sullenger do not appear to contain a non-native processing element.

Applicants further point out that *contra* to assertions made in the Office Action dated 2/16/99, a ribozyme would not be considered to be a "processing element". As recited in amended claim 245, the "processing element" used in the method of the present invention is substantially removed from the nucleic acid product during processing of the nucleic acid product. This does not occur with a ribozyme.

In view of the above arguments and the amendment of claim 245, Applicants assert that the rejections over Sullenger have been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

Hurwitz

Claims 245-251 have been rejected under 35 U.S.C. 102(e) as being anticipated by Hurwitz. It was asserted that Applicant has not provided any supporting evidence as to how the invention taught by Hurwitz neither discloses nor suggests the instant invention as broadly claimed. Furthermore, it is asserted that Hurwitz teach selective use of introns in an expressed gene for increased expression of the gene in a mammalian cell, specifically where the product is human serum albumin.

Applicants respectfully traverse the rejection. First, Applicants would like to clarify the teaching of Hurwitz. The construct of Hurwitz contains a sequence encoding human serum albumin and at least one intron in the naturally occurring HSA gene. Therefore, the construct of Hurwitz, in contrast to the construct of the present invention, does contain a native processing element. There is no disclosure in Hurwitz that the construct contains any non-native processing elements. Actually, it appears required in Hurwitz that the construct must contain at least one native intron. In contrast, in the construct used in the method of the present invention, the construct contains a nucleic acid sequence of interest and a **non-native** processing element.

It is evident that claims 245-251 are not anticipated by Hurwitz Therefore, Applicants respectfully request that the rejection under 35 U.S.C. §102(e) be withdrawn.

DeYoung

Claims 255-260 have been rejected under 35 U.S.C. 102(b) as being anticipated by DeYoung. It is asserted that Applicants do not address how DeYoung does not teach nor suggest the claimed invention. It is asserted in the

Office Action dated 2/16/99 that DeYoung teaches expression of ribozymes imbedded in a U1 sequence and under the control of a T7 promoter. Furthermore, it is asserted in the Office Action that ribozymes are known in the art to have a processing function and also have an inherent half-life and are therefore removed.

Applicants respectfully traverse the rejection. The constructs used in the method of the present invention can be distinguished from the vectors and systems that are taught by DeYoung. Specifically, DeYoung teaches the use of recombinantly expressed ribozyme to cleave ANF at various GUC or GUA sites. These GUC and GUA sites are endogenous and native to ANF. Furthermore, the ribozyme was not coexpressed with the ANF.

Applicants further note that the ribozyme was placed between initiation and termination sequences of U1 snRNA. These U1 sequences were not alt all acting as processing elements. Ribozyme is not a processing element that is substantially removed during processing.

Applicants further point out that *contra* to assertions made in the Office Action dated 2/19/99, a ribozyme would not be considered to be a "processing element". As recited in amended claim 245, the "processing element" used in the method of the present invention is substantially removed from the nucleic acid product during processing of the nucleic acid product. This does not occur with a ribozyme.

Clearly, DeYoung does not teach a vector containing all of the elements of the claimed constructs used in the method of the present invention. Therefore, claims 245-251 are not anticipated by DeYoung and the rejection of the claims under 35 U.S.C. §102(b) should be withdrawn.

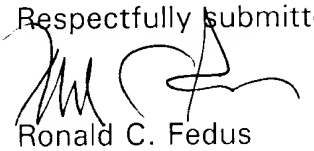
SUMMARY AND CONCLUSIONS

Claims 245-251 are presented for further examination. No claims have been added by this paper.

No fee or fees are believed due in connection with this paper. In the event that any fee or fees are due, however, The Patent and Trademark Office is hereby authorized to charge the amount of any such fee(s) to Deposit Account -5-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,



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AMENDED CLAIMS-MARKED UP VERSION

245 (Amended) A process for selectively expressing a nucleic acid product in a cell, which product requires processing for functioning, said process comprising;

(i) providing a nucleic acid construct which when introduced into a cell produces a nucleic acid product comprising a non-native processing element, which when in a compatible cell, said processing element is substantially removed from the nucleic acid product during processing of the nucleic acid product and

(ii) introducing said construct into said cell.

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